myeloid leukemia, colon cancer, endometrial carcinoma, lung cancer, ovarian cancer, cervical cancer, osteosarcoma and lymphoma, which method comprises administering to the subject an effective amount of paclitaxel and an effective amount of C_6-ceramide, sequentially or concomitantly.

13. ~~32.~~ (New) The method of claim 12 ~~31~~, wherein paclitaxel is first administered and C_6-ceramide is subsequently administered to the subject.

14. ~~33.~~ (New) The method of claim 12 ~~31~~, wherein C_6-ceramide is first administered and paclitaxel is subsequently administered to the subject.

REMARKS

Claims 1-18 are presently pending. Applicants have hereinabove canceled claims 1-18 without prejudice, and added new claims 20-33. New claims 20-33 have been added in order to incorporate certain format changes. Upon entry of this Amendment, claims 20-33 will be pending and under examination.

New claims 20-24 correspond to claims 1, 4, 5, 8 and 9, respectively. New claims 25-33 correspond to claims 2, 4, 5 and 8-13, respectively. Features recited in claims 3, 6 and 7 have been incorporated into claims 20 and 25. Features recited in claims 14 and 15 have been incorporated into claim 31. Features recited within claims 16 and 17 have been incorporated into claims 20 and 25, respectively. Finally, features recited in claim 18 have been incorporated into claim 30.

Support for new claims 20 and 25 can be found in the specification at, inter alia, page 2, lines 31-34; page 10, line 29 through page 11, line 15; page 15, lines 7-22; page 32, line 33 through page 33, line 9; and page 33, line 37 through page 34, line 5. Support for new claim 30 can be found in the specification at, inter alia, page 10, line 29 through page 11, line 15; page 13, lines 3-8; and page 32, line 33 through page 33, line 9. Support for new claim 31 may be found in the specification at, inter alia, page 11, lines 24-35, and page 32, line 33 through page 33, line 9. Support for "resulting apoptosis" in claim 20 can be found in the specification at, inter alia, page 22, line 6 and page 40, line 36. Support for "resulting decrease in size of the tumor" in claim 25 can be found in the specification at, inter alia, page 33, lines 5-9. The remaining changes to the claims merely introduce additional grammatical and format changes. Applicants maintain that these amendments raise no issue of new matter.

In view of the arguments set forth below, applicants maintain that the rejections made in the March 16, 2001 Final Office Action have been overcome, and respectfully request that the Examiner reconsider and withdraw the same.

Formalities

In their August 14, 2000 Amendment, applicants elected with traverse to prosecute at this time the combination of C_6-ceramide and taxol. The Examiner stated that the claims are still being examined as they read on the elected combination, and that cancellation of the non-elected combinations is now required.

In response, applicants point out that the claims as amended are directed solely to this combination.

The Claimed Invention

This invention provides new methods and compositions for decreasing tumor size and inducing tumor cell apoptosis. The claimed methods and compositions are surprisingly advantageous in that they employ the unexpectedly effective combination of paclitaxel and C_6-ceramide. In particular, in this invention, the resulting apoptosis and tumor size reduction caused by the paclitaxel and C_6-ceramide combination is greater than that caused by either agent alone.

Rejections Under 35 U.S.C. §112, First Paragraph

The Examiner rejected claims 1, 2 and 4-18 under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for the specific tumor and/or cancer disclosed, allegedly does not enable the term "tumor" and/or "cancer." The Examiner stated that the terms "tumor cells" in claims 1, 2-11, 16 and 18, and "cancer" in claims 11-15, lack clear exemplary support. The correlation between the rejected claims and the new claims is set forth above.

In response, applicants respectfully traverse this rejection. Applicants point out that the term "tumor cell" does not appear in the claims, as amended. The terms "tumor" and "cancer" also do not appear absent further enumeration. Specifically, claims 20, 25 and 30 recite specific types of tumor cells, and claim 31 recites specific types of cancer. Applicants maintain that the claims reciting

specific types of tumor cells and cancers are enabled, since one of ordinary skill would know how to practice the claimed methods and make and use the claimed pharmaceutical combination.

The Examiner also rejected claims 1-13 and 15 under 35 U.S.C. §112, first paragraph, because the specification while enabling for the specific antitumor chemotherapeutic agent and ceramide disclosed, allegedly does not enable "antitumor chemotherapeutic agents" and "a ceramide."

In response, applicants respectfully traverse the Examiner's rejection. New claims 20-33 lack the terms "antitumor chemotherapeutic agent" and "a ceramide." Instead, new claims 20-33 are directed solely to paclitaxel and C_6-ceramide.

In view of the above remarks, applicants maintain that new claims 20-33 satisfy the requirements of 35 U.S.C. §112, first paragraph.

Rejection Under 35 U.S.C. §103(a)

The Examiner rejected claims 1-18 under 35 U.S.C. §103(a) as allegedly unpatentable over WO 94/04541 ("'541 application") taken with Jayaden et al. for the reasons set forth in the September 28, 2000 Office Action. Claims 1-18 have been replaced with new claims 20-33 discussed above.

In response, applicants respectfully traverse the Examiner's rejection. The correlation between the rejected claims and the new claims is set forth above.

The Examiner has failed to make a *prima facie* case of obviousness.

To reiterate, each of new claims 20-33 has as elements (i) the combination of paclitaxel and C_6-ceramide which (ii) causes apoptosis and reduces tumor size at rate unexpectedly greater than that caused by either agent alone.

Briefly, the '541 application teaches a combination of sphingosine and taxol (also referred to as paclitaxel). Jaydev et al. teach that C_6-ceramide can induce G_0/G_1 arrest along with apoptosis. As the Examiner concedes, neither reference teaches or suggests the combination of paclitaxel and C_6-ceramide of this invention.

To establish a *prima facie* case of obviousness, the Examiner must demonstrate three things with respect to each claim. First the cited references, when combined, teach or suggest every element of the claim. Second, one of ordinary skill would have been motivated to combine the teachings of the cited references at the time of the invention. And third, there would have been a reasonable expectation that the claimed invention would succeed.

First, neither Jaydev et al. nor the '541 application teaches or suggests each and every element of the instant claims. Neither reference teaches or suggests combining paclitaxel and C_6-ceramide, or that such combination, whether sequential or concomitant, results in apoptosis greater than that caused by either agent alone. Thus, to support a case of *prima facie* obviousness, these references would have to teach or suggest these elements. They do not.

Second, the cited references teach away from the claimed invention. Specifically, the Examiner takes an untenable position in suggesting that sphingosine and ceramide are physiologically equivalent, and would therefore be equally effective anti-cancer agents when combined with taxol. The facts indicate that quite the opposite is true.

Spingosine and C_6-ceramide are entirely different molecules. They are required for different cellular functions, having different effectors and inducing different cellular effects.

More importantly, ceramide is not interchangeable with sphingosine in connection with many cellular functions, especially cellular apoptosis.

In support of this position, applicants annex hereto as Exhibit B a copy of Ping et al. This reference shows that in neuronal cells, even in the presence of nerve growth factor (NGF), ceramide causes apoptosis in the presence of a ceramidase inhibitor. In startling contrast, however, sphingosine promotes survival in these cells. The reference also shows that in these cells, certain ceramide analogs also promote survival in the presence of ceramidase inhibitors. Therefore, in view of Ping et al., one of ordinary skill would not have been motivated to attribute the characteristics of ceramide to spingosine, and therefore would not have been motivated to combine the teachings of the '541 application and Jaydev et al.

Further, one of skill in the art would not have had a reasonable expectation that the claimed invention would succeed based on the above-cited references, since again, spingosine and ceramide are

different molecules with different cellular means of action.

For these reasons, the Examiner has failed to establish the *prima facie* obviousness of claims 20-33 over the '541 application and Jaydev et al. Likewise, applicants respectfully maintain that the rejected claims would not have been obvious over these references.

In view of the above remarks, applicants maintain that claims 20-33 satify the requirements of 35 U.S.C. §103(a).

Supplemental Information Disclosure Statement

This Supplemental Information Disclosure Statement is submitted as a supplement to the Information Disclosure Statement filed on August 13, 1999.

In accordance with their duty of disclosure under 37 C.F.R. §1.56, applicants direct the Examiner's attention to Ping SE and Barrett GL, "Ceramide can induce cell death in sensory neurons, whereas certain ceramide analogues and sphingosine promote survival", *J Neurosci Res.* Vol. 54, No. 2, October 15, 1998, pages 206-213 (Exhibit B), which is listed on Form PTO-1449 (Exhibit A).

Applicants request that the Examiner make this document of record in the subject application.

In view of the amendments and remarks made herein, applicants maintain that the claims pending in this application are in condition for allowance. Accordingly allowance is respectfully requested.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:

Assistant Commissioner for Patents, Washington, D.C. 20231.

6/15/01
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